REMARKS

Applicant appreciates the Examiner's response and confirms the election of Group I as provided in the restriction requirement and amendment filed on March 25, 2002. Accordingly, Claims 1-5, 7-13, 15-29, and 31-36 are pending in the present application and currently stand rejected. In light of the present amendments and the provided remarks, Applicant respectfully requests reconsideration of the present application.

I. Objections to the Specification

The specification has been amended to remove the embedded hyperlinks and/or other form of browser executable code as provided in the originally filed specification. Applicant respectfully requests reconsideration of the specification.

II. Rejection of Claims based on 35 U.S.C. 112, first paragraph

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification. In accordance with the Examiner's rejection, Applicant suggests that support for the newly amended claim is provided throughout the specification, more particularly on pages 7 and 8, wherein it is provided that DNA sequence data as obtained in step (d) could be compared to that obtained from theoretical peptide mass fingerprinting. In light of the amended claims and provided support within the specification, Applicant request reconsideration of the rejected claim.

III. **Rejection of Claims 1-5, 7-13, 15-29, and 31-36 under 35 U.S.C. 112, second paragraph**

Claims 1-5, 7-13, 15-29, and 31-36 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In light of the provided amendments and the following remarks, Applicant respectfully requests reconsideration of the rejections.

In accordance with the Examiner's remarks, Claims 1, 2, 4, 5, 7, 8, 12, 13, 17, 18, 29 and 34 have been amended to overcome the Examiner's rejections. Claims 10, 11, and 22-27 have been deleted and claims 37-46 have been added. In light of the amendments made to the claims, Applicant respectfully requests reconsideration of the rejections.

In particular, Claim 1 has been amended to address the Examiner's rejections and provide further clarification. According to the Examiner, it would not have been clear to one of ordinary skill to "select or identify an antibody in method step (e) that has already been selected in method step (b). The amended claim should provide further clarification. The amendment is provided to clarify that the method can be applied to the type of technology wherein a select antibody is used and it is not necessary to proceed through the screening process, such as seen in phage display technology. Claim 1 has further been amended to address the Examiner's remarks regarding the difference between steps C(i)/C(ii) and B(ii). More particularly, the amendment to Claim 1 exemplifies that antibodies are used individually in step C(i) whereas in step B(ii) the antibodies are not used individually. Claim 1 has further been amended to claim the use of a mixture of proteins, as compared to only one protein.

The Examiner suggested in part 3D of the Office Action that the sequence of steps of the present method for identifying an antibody that binds to a protein does not appear to be productive. According to the present invention, the screening method of individual antibodies occurs by adding one or more proteins to the antibody and then removing any unbound proteins. Subsequently, the bound proteins are eluted by an eluting agent resulting in the desired target proteins. As described, this screening method is highly productive and Applicant requests reconsideration. In general, the proteins in method step C(ii) are eluted from antibody protein complexes. The proteins may be eluted from a variety of antibody-protein complexes in various forms as known in the art and are not limited to one particular complex.

The Examiner further rejected Claim 1 as being incomplete for omitting essential steps. Applicant believes that all necessary steps are present. For example, although a specific protein is of interest, it is not required that it is known or has been identified. The present invention may be used to screen for antibodies that recognize proteins by matching profiles exhibited by the proteins of interest. Therefore, it is not necessary to know the specific sequence of the protein, as suggested by the Examiner. In addition, Applicant has provided references that review methods for mass spectrometry based characterization of proteins. It is therefore submitted that one of ordinary skill in the art would know the meets and bounds of the term "mass spectrometry based characterization". Applicant believes that in light of the provided references and the current state of the art, the rejection of Claims 1, 15, 16, 34, and 36 have been overcome.

Additional amendments have been made to provide further clarification and in response to the Examiner's rejections. Claim 2 has been amended to provide an

electrophoresis step that is performed previous to the screening steps of Claim 1. In particular, the proteins are resolved by 2D electrophoresis, which is known within the art by one of ordinary skill. Claim 4 has been amended to correct a typographical informality, thereby correcting the lack of antecedent basis present in the claim. The rejections of Claims 5 and 29 have been overcome by deleting the characterization of the method as the "shotgun" method. Claim 7 has been amended to provide that when antibodies are generated in step B(i), they are subsequently immobilized. Claim 8 has been amended to provide that once the antibodies are immobilized, the nitrocellulose or PDVF is treated. Consequently, the remaining binding sites that are blocked, are those that have not been previously adhered to by the binding proteins.

The Examiner has rejected Claims 12 and 13, as omitting essential steps, such as method steps that would allow one to obtain a theoretical peptide mass profile. It is suggested by the Examiner that one cannot obtain such a profile for an unknown protein. Applicant suggests that one can obtain a theoretical profile from a DNA sequence, although the DNA sequence may or may not encode protein. The process of obtaining a theoretical peptide mass profile is known in the art and therefore it is suggested by the Applicant that gaps within the claim are not present. The Examiner further rejects Claim 12 on the basis that one of ordinary skill in the art would not be able to interpret the claim because there is no limitation requiring the mass profiles obtained in steps (b) and (d) to include profiles from the same protein or complex mixtures of proteins. Applicant suggests that the mass profiles obtained in steps (b) and (d) of particular antibodies are used to screen for similar proteins between different biological extracts. Therefore, it would not be necessary to limit the mass profiles of the proteins to include those used in

the preparation of profiles. Similarly, Claim 13 provides in method step (c) that a complex protein mixture can be used to generate antibodies against a protein that is present in a different complex protein mixture. As previously suggested, individual proteins may be present in two different complex mixtures, such as different biological extracts (i.e. brain and liver). Therefore, it is applicable that the process would allow the comparison of proteins from different complex protein mixtures. In addition, antibodies from one complex mixtures may be applied to another, due to the presence of similar proteins. Claim 13 has been amended for further clarification, with regards to method step (f).

Claim 15 has been rejected by the Examiner as being incomplete for omitting essential steps. As previously suggested with regards to Claims 12 and 13, one can obtain a theoretical profile from a DNA sequences, although the DNA sequences may or may not encode the protein. It is further suggested that the process of obtaining a theoretical peptide mass profile is known in the art and that the gaps within the claim, as suggested by the Examiner, are not present. Applicant has further provided the enclosed references to suggest that one of ordinary skill in the art would be able to determine what characterizations are included within the scope of the claims.

Examiner rejected Claim 16 as having a typographical error in line 1. Applicant draws the Examiner's attention to the amended Claim 16 as filed in the response of March 25, 2002. It seems that the previously filed amendment removed the Examiner's rejection regarding the typographical error. In addition, the Examiner suggested that Claim 16 is incomplete for omitting essential steps. In light of the previous remarks

provided for Claims 12, 13, and 15, Applicant believes that the rejection has been responded to.

Claims 12, 17, and 19 were further rejected for lacking antecedent basis or needing further clarification. In light of the amendment provided, Applicant believes that each of these rejections raised by the Examiner have been answered and overcome.

Examiner rejected claims 31-33 and 35 for lack of clarification. The dependent claims suggesting that mass spectrometry based characterization is achieved by a peptide mass fingerprint is applicable to either of the references to mass spectrometry. The claims are provided to suggest a form of mass spectrometry that can be used throughout the process. The reference to peptide mass fingerprinting is not intended to solely limit the mass spectrometry based characterization to such means.

Lastly, Claim 34 has been amended in accordance to with the metes and bounds of the specification and of those skilled in the art.

Claims 37-46 have been added to further clarify the claims and in response to the Examiner's rejection of Claims 10 and 22-27 for lack of antecedent basis. Applicant respectfully requests consideration of the newly added claims.

In light of the amendments provided and the above remarks, Applicant suggests that the Examiner's rejections based on 35 USC 112, second paragraph, have been removed. Applicant respectfully requests reconsideration of the application and the amended claims.

IV. Claims 1, 4, 13, 16, 17, 31, and 33-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Yates, III et al. (US Patent No. 6,017,693 issued January 2000)

Claims 1, 4, 13, 16, 17, 31, and 33-35 stand rejected under 35 U.S.C. 102(e) as being anticipated by Yates, III et al., US Patent No. 6,017,693. Applicant respectfully traverses the rejection.

According to the Examiner the Yates reference discloses mass spectrometry-based methods for identifying proteins and application of the methods. Applicant believes that the Yates invention provides a method of using mass spectrometry data of the masses of peptides and sub-fragments thereof derived from a protein compared with theoretical masses calculated from DNA and protein sequence databases. Yates describes how this method could be used to identify and characterize a protein that has been received by affinity capture using an antibody of known or anticipated specificity as determined by conventional antibody screening processes.

In contrast, the present invention is directed to the screening and characterizing of antibodies that bind to proteins, whereas the Yates is directed to finding out about the proteins per se. Using the Yates reference, one could not screen antibodies as described in the present invention. Furthermore, the present invention does not require access to the purified protein or epitope, as required in the Yates reference, because the characterization is used to determine the specificity of the antibody, not the protein. It is therefore submitted by the Applicant that the Yates reference does not anticipate or render obvious the present invention.

In light of the above remarks, Applicant respectfully requests reconsideration of the application and the amended claims.

V. CONCLUSION

In view of the foregoing amendments and submissions, Applicant respectfully requests that the rejection of pending claims 1-5, 7-13, 15-29, and 31-36 be withdrawn. Applicant requests consideration of the amended claims 1, 2, 4, 5, 7, 8, 12 13, 17, 18, 29, and 34 and newly added claims 37-46. If the Examiner should have any questions, please contact the undersigned for any further clarification. Applicant hereby requests further consideration of the application.

Respectfully submitted,

Date 12/17/02

By: _____

Robert L. Kelly
Reg. No. 31,843
Attorney for Applicant
Phone: 248-203-0849
Fax: 248-203-0763
DYKEMA GOSSETT PLLC
39577 Woodward Ave, Suite 300
Bloomfield Hills, MI 48304-2820

CERTIFICATE OF EXPRESS MAILING

I hereby certify that the enclosed Amendment in Response to Office Action is being deposited with the United States Postal Service as Express Mail No. ET931276685US, postage prepaid, in an envelope addressed to the Assistant Commissioner for Patents, Washington, DC 20231, on this 17th day of December, 2002.

Patricia A. Kniola

Patricia A. Kniola

Appendix A

(A Copy of the Marked Up Version)

The last few years have heralded an unprecedented increase in gene sequencing and identification as exemplified by the announcement of the complete genome sequence of prokaryotic and eukaryotic cells and organisms including the model eukaryote C. elegans ([see http://www/nih/gov/new/pr/dec98/nhgri-09.htm;] Science, 11 Dec 1998). The sequencing of the human genome continues to accelerate with completion projected for 3-4 years time. This growing DNA sequence data is being used as a platform for the systematic investigation of gene (mRNA) expression and function. Such investigation combined with associated informatics are transforming basic biological research and will transform the drug discovery, development and delivery processes. However, it has become increasingly apparent that DNA sequence data in itself often provides little information about the function of the encoded protein products. Furthermore, measurement of gene expression at the mRNA level does not always give an accurate representation of the expression of the corresponding proteins nor indeed of the extent to which they may be post-translationally modified. Importantly, it is predominantly proteins that execute biological function. Hence, there is a growing desire to analyse, in a systematic and comprehensive manner, the expression and activity of the protein products of an organism's genome – this aim provides a working definition of proteome analysis (or proteomics) (see Pennington et al. Proteome analysis: from protein characterization to biological function. Trends Cell Biol. 7, 168-173 and references therein). It is important to emphasise that the activity of individual proteins may be regulated by a number of

different mechanisms including their level of expression within individual tissues or cells, the extent and type of post-translational modification, their subcellular localization and their interactions with other proteins. Proteomics therefore encompasses a broad range of experimental approaches.

(Page 20, lines 19-26)

The predominant peptide masses from the spectrum in Figure 5A and 5B were selected 'blind' (after subtraction of peaks shown to originate from residual non-specific protein binding by use of an appropriate control – proteins recovered from wells in which no antibody has been immobilized) and used to search protein sequences databases using publicly available software [(for example see http://www.mann.embl-heidelberg.de/Services/PeptideSearch)]. Again BSA was identified as the 1st ranging protein.

Appendix B
(A Copy of the Marked Up Version)

1. (Twice Amended)) A method of selection and/or identifying one or more protein affinity ligands, wherein the affinity ligands are antibodies, that bind to one or more proteins of interest, comprising the steps of:

(A) obtaining a real or theoretical mass spectrometry based characterization of the one or more proteins by either:

i. Subjecting the one or more proteins to a mass spectrometry based characterization; or

ii. Predicting the mass spectrometry based characterization from known data;

(F) utilizing the one or more proteins either individually or as a mixture to:

j. Generate one or more antibodies thereto by immunization; and/or

ii. Select, using a single or multiple rounds of binding, one or more antibodies thereto;

(G) screening to one or more antibodies generated in step B(i) and/or [the one or more] multiple antibodies selected by step (B)(ii) by:

j. adding a mixture of proteins or the one or more proteins individually [or as a mixture of proteins] to the one or more antibodies generated in step (B)(i) or the one or more antibodies selected in step (B)(ii), each antibody being used individually, and

ii. after removing any proteins which have not bound, eluting the at least one protein has bound;

(H) subjecting the at least one eluted protein to mass spectrometry based characterization; and

(I) by comparing the mass spectrometry based characterization obtains in steps (A) and (D), selecting and/or identifying that at least one antibody that binds to the one or more proteins of interest.

2. (Once Amended) A method as claimed in claim 1 wherein the one or more proteins of interest [are] have been previously resolved by 2D electrophoresis.

4. (Twice Amended) A method as claimed in claim 1 wherein the one [of] or more proteins of interest are present in a mixture of proteins.

5. (Twice Amended) A method as claimed in claim 1 wherein the method is a [shotgun] method for selecting and identifying protein affinity ligands to a plurality of proteins.

7. (Twice Amended) A method as claimed in claim 1 wherein the antibodies optionally generated in step (B)(i) are immobilized on a support comprising nitrocellulose or PVDF.

8. (Once Amended) A method as claimed in claim 7 wherein the support upon which the antibodies are immobilised and the nitrocellulose or PVDF are treated with an oligosaccharide or polyvinylpyrrolidine solution to block any remaining binding sites.

12. (Once Amended) A method generating monoclonal antibodies to one or more targeted proteins comprising the steps of:

(a) resolving a complex protein mixture;

(b) subjecting the resolved protein(s) to peptide mass fingerprinting to obtain a peptide mass profile or obtain a theoretical peptide mass profile;

(c) utilizing one or more of the resolved proteins to generate one or more monoclonal antibodies thereto;

(d) adding the or another complex protein mixture to the one or more monoclonal antibodies generated in Step (c), to select those proteins which bind the one or more monoclonal antibodies, and subjecting the selected proteins(s) to peptide mass fingerprinting to obtain a peptide mass profile;

(e) comparing the peptide mass profiles obtained in steps (b) and (d); and

(f) selecting one or more monoclonal antibodies [hybridoma clones] of interest.

13. (Once Amended) A method of generating an antibody library comprising the steps of:

(a) resolving a complex protein mixture and subjecting the resolved protein(s) to peptide mass finger printing to obtain a peptide mass profile; or

(b) obtaining a theoretical peptide mass profile for a protein which is sought;

(c) utilizing the or the other complex protein mixture to generate one or more monoclonal antibodies thereto;

(d) adding the one or the other complex protein mixture to the one or more monoclonal antibodies generated in Step (c) to select those proteins which bind the one or

more monoclonal antibodies, and subjecting the selected protein(s) to peptide mass fingerprinting to obtain a peptide mass profile;

(e) comparing the peptide mass profiles obtained in steps (a or b) and (d); and

(f) identifying the monoclonal antibodies of [potential] interest [for a monoclonal antibody library].

17. (Twice Amended) A method as claimed in claims 1, 2, 7, 8, or 9[, 10, 19, 20, 21, 22, 23, 24, 25, 26, or 27] wherein the mass spectrometry based characterization [peptide mass fingerprint] is obtained by mass spectrometry.

18. (Twice Amended) A method as claimed in claims 1, 2, 7, 8, or 9 [, 10, 19, 20, 21, 22, 23, 24, 25, 26, or 27] further comprising the use of automated well plate handling technology and automated high-throughput mass spectrometry.

29. (Once Amended) A method as claimed in claim 2 wherein the method is [shotgun] method for selecting and identifying protein affinity ligands to a plurality of proteins.

34. (Once Amended) A method of selecting and/or identifying at least one antibody which binds at least one protein of interest, comprising the steps of:

(a) obtaining a theoretical [pre-selected] mass spectrometry-based characterization of a target protein [to serve as a reference standard];

(b) providing an antibody which selectively binds to said target protein;

(c) isolating and collecting said target protein through affinity binding with said antibody;

(d) analyzing said collected target protein for said pre-selected mass spectrometry-based characterization; and

(e) comparing the mass spectrometry-based characterization obtained in step (d) with the theoretical mass spectrometry-based characterization [reference standard] of step (a).

37. (New) A method as claimed in claim 1 wherein an eluting agent is further provided for eluting protein from antibody-protein complexes.

38. (New) A method as claimed in claim 37 wherein the eluting agent is formic acid.

39. (New) A method as claimed in claim 8 wherein an eluting agent is further provided for eluting protein from antibody-protein complexes.

40. (New) A method as claimed in claim 39 wherein the eluting agent is formic acid.

41. (New) A method as claimed in claim 19 wherein an eluting agent is further provided for eluting protein from antibody-protein complexes.

42. (New) A method as claimed in claim 41 wherein the eluting agent is formic acid.

43. (New) A method as claimed in claim 20 wherein an eluting agent is further provided for eluting protein from antibody-protein complexes.

44. (New) A method as claimed in claim 43 wherein the eluting agent is formic acid.

45. (New) A method as claimed in claim 21 wherein an eluting agent is further provided for eluting protein from antibody-protein complexes.

46. (New) A method as claimed in claim 45 wherein the eluting agent is formic acid.

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